REMARKS

Status of the Claims

Claims 1-3 and 5-24 are pending in the application. Claims 1-3 and 5-24 stand rejected. Claims 1-3, 9, 10 and 12 are amended herein.

Claim Rejections

35 U.S.C. § 112, first paragraph

Claims 1-3, 5-14, and 24 stand rejected under § 112, first paragraph, for failing to comply with the written description requirement.

The Examiner also argues that the phrase "without separation of said red blood cells from said extracellular heme-colored blood substitute prior to analysis" in claims 1 and 9 is not supported by the specification and therefore constitutes new matter. Applicants respectfully disagree. The test for written description compliance is not whether Applicants have exactly described this feature, but rather whether the specification reasonably conveys to the skilled artisan that Applicants were in "possession" of the claimed embodiment, i.e., performing the analysis "without separation of said red blood cells from said extracellular heme-colored blood substitute prior to analysis." See Vas-Cath v. Mahurkar, 935 F.2d 1555, 1563 (Fed. Cir. 1991). The skilled artisan, upon reading Applicants entire disclosure, would unambiguously understand that applicant was in possession of embodiments of the claimed method where a sample is analyzed on a cell-by-cell hematology analyzer without prior separation of the cellular components from the extracellular components. For example, Applicants point out that there is no step of separating red blood cells either explicitly or implicitly stated anywhere in the specification. Rather than being an omission of this feature, one skilled in the art would understand this to be an implicit disclosure of this feature. This is clear from reference to well-

known hematology analyzers which are recognized as not requiring prior separation of the sample components. For example, in paragraph [0026] of the specification, it is stated that "automated hematology analyzers produced by and commercially available from Bayer Corporation, the assignee hereof, have been found to be able to directly determine and measure the concentration of exogenous, i.e., extracellular, hemoglobin in a sample" (emphasis added). At the end of the same paragraph this statement appears "the Bayer H™ series of hematology analyzer instruments and the Bayer ADVIA® series of hematology analyzer instrument systems (e.g., ADVIA 120®) have the capability of performing quantitative analysis on the total hemoglobin content of blood and of distinguishing the hemoglobin component derived from red blood cells from that derived from the plasma." The totality of the disclosure would therefore make clear to one skilled the art that the measurements of intracellular and extracellular hemoglobin in the claimed invention are made without separating the blood sample prior to submitting it to the analyzer.

Further, in example 1 of the application it is explicitly stated that "extracellular (or non-cell derived) hemoglobin" was added to the blood samples before analysis (paragraph [0052], first sentence). This is the antithesis of prior separation of components, and is fully supportive of a limit requiring no prior separation. Therefore Applicants assert that it would be readily apparent to one skilled in the art that the claimed invention is to be performed "without separation of said red blood cells from said extracellular heme-colored blood substitute prior to analysis." For the foregoing reasons, Applicants respectfully request withdrawal of the grounds of rejection.

In the Advisory Action dated December 9, 2005, the examiner indicated that the following arguments regarding "extracellular to said red blood cells" were persuasive. The

arguments are repeated here in order to be fully responsive. The Examiner also argues in the September 16 Office Action that the phrase "extracellular to said red blood cells" in claims 1 and 9 is not supported by the specification and therefore constitutes new matter. Applicants respectfully disagree. The has Examiner acknowledged that there is support for "generic extracellular limitations." Given that there is support, generally, for "extracellular" hemoglobin, there is clearly support for hemoglobin "extracellular to said red blood cells" because (1) the term "extracellular" by definition means outside of a cell, and (2) red blood cells are clearly described in the application as one of the cellular components of blood. Therefore, the skilled artisan would immediately understand that Applicants were in possession of embodiments wherein hemoglobin is "extracellular to said red blood cells." That is all that is required to satisfy the written description requirement. See Vas-Cath v. Mahurkar, 935 F.2d 1555, 1563 (Fed. Cir. 1991). Nonetheless, in order to advance prosecution on the merits, this language has been removed from claims 1 and 9. This amendment does not alter the scope of the claims and is therefore merely editorial in nature. In light of this amendment, the rejection is rendered moot.

35 U.S.C. § 112, second paragraph

Claims 1-3, 5-14 and 34 have been rejected by the examiner for unclear claim language in reference to "blood sample" and "other sample comprising red blood cells." The preambles of claims 1 and 9 have been amended to delete reference to a "blood sample" in order to clarify the claim language. As amended, the claims are directed to a method of correcting interference in MCH and MCHC in a "sample comprising red blood cells." This amendment does not alter the scope of the claims because a "blood sample" is an example of the generic "sample comprising red blood cells," as it is well know that blood comprises red blood cells. As such, this amendment is merely editorial.

Claims 1 and 9 have also been amended to recite "analyzing said blood sample on an automated cell-by-cell hematology analyzer" as a positive method step in response to the Examiner's comments.

Based on the above amendments, Applicants respectfully request withdrawal of these rejections.

35 U.S.C. § 103

The Examiner has rejected claims 1-3 and 5-24 as being unpatentable over Chupp et al. (US 5,631,165) in view of Chang et al. (US 5,200,323), Samsoondar (WO 98/39634) and Rodriguez et al. (US 6,228,652).

Applicants respectfully assert that no combination of the cited references is adequate to teach or suggest every limitation of the claimed methods. The references simply cannot be combined to arrive at the claimed methods.

Briefly, the present application is directed to methods for obtaining corrected values of mean cell hemoglobin content (MCH) and mean cell hemoglobin concentration (MCHC) in blood samples containing exogenous heme-colored blood substitutes. The blood samples comprise two types of hemoglobin: (1) "intracellular" hemoglobin or, synonymously, "cellular" hemoglobin[1] (hereinafter collectively, "intracellular hemoglobin"), and (2) "extracellular" hemoglobin.

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[1] The Examiner asserts that Applicants' specification does not contain a definition of the term "cellular hemoglobin." Applicants point to the phrase "intracellular (or cellular) hemoglobin" in the first sentence of paragraph [0042] of the specification. This passage clearly equates "intracellular hemoglobin" and "cellular hemoglobin" and thus it would be unambiguously clear that "cellular hemoglobin" is hemoglobin that is within a cell. To clarify the claim language, and to advance prosecution of this case on the merits, the terms "cellular hemoglobin" has been changed in the claims to "intracellular hemoglobin." This amendment does not alter the scope of the claims, as the skilled artisan would recognize that Applicants have clearly equated the two terms.

To properly understand the claimed invention, it is critical to understand the terminology employed. The terms "intracellular" refers to hemoglobin that is contained within blood cells. At all times during the measurement of "intracellular" hemoglobin according to the invention, the "intracellular" hemoglobin is within the cells. "Intracellular" hemoglobin may be envisaged as natural (or endogenous) hemoglobin made by and contained within the blood cells.

In treating various conditions, it may be desirable to provide a patient with a blood substitute which contains artificial (or exogenous) hemoglobin which is not "intracellular," but rather is "extracellular" because it is located in the plasma or serum rather than within a blood cell.

Thus one sample (i.e., a "sample comprising red blood cells") can simultaneously contain both "intracellular" hemoglobin which is located with the blood cells, and "extracellular" hemoglobin, which is located in the plasma or serum. It is important for physicians to be able to determine how much of each type of hemoglobin is present within a sample. Conventionally, in the analysis of blood samples for hemoglobin, the red blood cells are lysed before analysis. After being lysed, and thus at the time of analysis, the hemoglobin that was in the cells looses its identity as "intracellular" hemoglobin and would be indistinguishable from "extracellular" hemoglobin. Therefore any value for MCH or MCHC derived from a measurement made under these conditions would be in error because it would include hemoglobin that was not from within the red blood cells. The present invention solves this problem by allowing the measurement of "intracellular" hemoglobin in the presence of "extracellular" hemoglobin.

The invention claimed in this application provides a method for measuring hemoglobin within red blood cells where the measurement is corrected for the presence of hemoglobin or hemoglobin substitutes in the sample that is outside of the red blood cells,

allowing for an accurate determination of MCH and MCHC. None of the cited references, alone or in combination, disclose or suggest a method for measuring "intracellular" hemoglobin in the presence of exogenously added "extracellular" hemoglobin.

The cited references are discussed briefly below.

Chupp

Chupp relates generally to the analysis of whole blood samples using a "conventional hematology analyzer integrated with a fluorescence cytometery analyzer" (Abstract). In the method disclosed in Chupp, hemoglobin is measured after the red blood cells are lysed. This point is critical. The skilled artisan would understand that after the red blood cells are lysed, the "intracellular" hemoglobin loses its identity as such and becomes indistinguishable from hemoglobin which was "extracellular" prior to lysis.

Thus, were one hypothetically to employ a blood sample comprising both "intracellular" and "extracellular" hemoglobin in the method of Chupp, a correct measure of "intracellular" hemoglobin could not be obtained. There is simply no teaching of a method for measuring "intracellular" hemoglobin in the presence of an extracellular hemoglobin or heme-colored blood substitute.

In reference to Chupp, the Examiner states that "[a] sample comprising lysed red blood cells would therefore necessarily comprise intracellular hemoglobin." As explained herein, this is not the case. The term "intracellular" means just that – i.e., that the hemoglobin is inside a blood cell. Once the cell is lysed, there is no longer "intracellular" hemoglobin. The fact that Chupp lyses the red blood cells before analysis renders Chupp wholly irrelevant to the present claims which require the measurement of intracellular hemoglobin – i.e., hemoglobin which is inside a blood cell at the time of measurement.

While it is clear that Chupp discloses hemoglobin that is intracellular in origin, Chupp has no way of distinguishing this "intracellular" hemoglobin from hemoglobin or hemoglobin substitutes that were present outside of the red cells prior to their being lysed. Therefore Chupp has no relevance to the claimed invention which is directed to the measurement of MCH and MCHC in the presence of exogenous blood substitutes.

Chang

Chang discloses a method of testing blood substitutes for safety before they are given to human patients. In Chang, a whole blood sample is taken from the patient and the red cells removed to make a plasma sample. The blood substitute is then added to the plasma sample to test if complement is activated (Abstract). It is important to note that the blood substitute is added to human plasma, which lacks cellular hemoglobin because the red cells have been removed. Thus, Chang does not describe a sample comprising "intracellular" and "extracellular" hemoglobin and certainly does not disclose a method for measuring the concentration of either intercellular or extracellular hemoglobin or how to correct hematology values based on the presence of blood substitutes in a sample. Applicants fails to see how Chang has any relevance to the pending claims beyond disclosing that blood substitutes exist in general.

Chang does not rectify the deficiencies of the other references, which alone or in combination, fail to teach or suggest a method for measuring "intracellular" hemoglobin in the presence of "extracellular" hemoglobin or heme-colored blood substitute.

Rodriguez

Rodriguez discloses a blood analyzing instrument for measuring "the DC volume, RF conductivity, light scattering and fluorescent characteristics of blood cells" (Abstract). The analyzer produces a report on the "cellular hemoglobin information for red blood cells and reticulocytes, mean volumes of the aforementioned cell types and derived parameters including

total hemoglobin for the sample" (column 13, lines 30-33). The disclosed analyzer can also measure "erythrocyte cell-by-cell hemoglobin" (column 13, line 38). Rodriguez does not disclose measuring the level of "intracellular" hemoglobin in the presence of extracellular hemoglobin.

Samsoondar

Samsoondar discloses a method "whereby the concentration of a blood substitute, such as cross-linked hemoglobin, in a serum or plasma specimen is rapidly and accurately identified and quantified" (emphasis added) (Abstract). Further, the method takes "the measured concentration of the blood substitute and uses it to correct for its effect, if any, on a measured analyte concentration e.g. serum/plasma total protein." However, Samsoondar does not teach or suggest measurement of "intracellular" hemoglobin in the presence of extracellular hemoglobin or blood substitutes as recited in the pending claims.

Rather, Samsoondar actually teaches away from the present invention by requiring separation of red blood cells from serum or plasma prior to the measurement of hemoglobin. In contrast, the claimed invention requires analysis "without separation of said red blood cells from said extracellular heme-colored blood substitute prior to analysis."

None of the cited references teach the measurement of intracellular hemoglobin in the presence of extracellular hemoglobin or a blood substitute.

Further, Applicants asserts that there is no motivation to combine the references in the manner suggested by the Examiner. In some cases the references even are in direct conflice with each other. Chupp requires the lysis of red cells before the measurement of hemoglobin while Rodriguez requires the cells to be whole. The Examiner has not pointed to any specific statements or disclosures in the references themselves that would lead the skilled

artisan to make the suggested combination, but rather offers the conclusory statement that "[o]ne of ordinary skill in the art reasonably would have expected success to combine these references, because the prior art references all deal with analyzing blood samples." This is not a legally sufficient reason to combine these references.

The Federal Circuit has held that "evidence of a suggestion, teaching, or motivation to combine may flow from the prior art references themselves, the knowledge of one of ordinary skill in the art, or, in some cases, from the nature of the problem to be solved." In re Dembiczak, 175 F.3d 994, 999 (Fed. Cir. 1999). However, the Court cautioned that:

> The range of sources available, however, does not diminish the requirement for actual evidence. That is, the showing must be clear and particular. . . . Broad conclusory statements regarding the teaching of multiple references, standing alone, are not "evidence."

(emphasis added) Id. The Examiner cannot properly rely on the fact that these references are all purportedly in the same field of endeavor as a motivation to combine them but rather must set forth a "clear and particular" showing of why the references would have been obvious to combine at the time the application was filed. The Examiner appears to be relying on an impermissible hindsight reconstruction of Applicants' invention, as none of the prior art cited is even concerned with measuring intracellular hemoglobin in the presence or exogenous blood substitutes.

Finally, Applicants note that the step of analyzing the blood sample on an automated cell-by-cell hematology analyzer has been amended herein to recite "without separation of said red blood cells from said extracellular heme-colored blood substitute prior to analysis" as an active method step in the body of claims 1 and 9 and thus further serves to differentiate the claimed invention from the prior art discussed herein.

Applicants assert that the foregoing amendments and remarks place the application in condition for allowance and request that these amendments be entered in the record and after due consideration a notice of allowance issued.

AUTHORIZATION

The Commissioner is hereby authorized to charge any additional fees which may be required for consideration of this Amendment to Deposit Account No. **13-4500**, Order No. 0708-4057. A DUPLICATE OF THIS DOCUMENT IS ATTACHED.

In the event that an extension of time is required, or which may be required in addition to that requested in a petition for an extension of time, the Commissioner is requested to grant a petition for that extension of time which is required to make this response timely and is hereby authorized to charge any fee for such an extension of time or credit any overpayment for an extension of time to Deposit Account No. **13-4500**, Order No. 0708-4057. A DUPLICATE OF THIS DOCUMENT IS ATTACHED.

Respectfully submitted,
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